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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,352	03/24/2006	Robert Hugh Bradbury	09963.0010	8785

22852 7590 10/28/2009

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
10/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,352	BRADBURY ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 31-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL ACTION

Applicant's amendment of 5-22-09 has been fully considered. Claim 30 is cancelled, and thus the rejection for "Use Claim" has been overcome. The rejections of 112/1st and 2nd paragraphs on "prodrug form thereof" have also been overcome by the deletion of said phrase. However, applicant's explanation for "anti-proliferative effect" is not persuasive. Thus, said rejection is maintained. Also, an updated search yields two relevant references that raise the following new ground of rejection.

Claims 1-29 and 31-34 are pending.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Scope of Enablement:** Claims 31, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating certain cancers such as breast, ovarian, colorectal, prostate, and lung cancer, does not reasonably provide enablement for a method of treating all proliferative disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;
(2) The amount of direction or guidance presented;
(3) The state of the prior art;
(4) The relative skill of those in the art;
(5) The predictability or unpredictability of the art;
(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 31 recites a "method for producing an anti-proliferative effect…" The term "proliferative effect" can be found in many types of tumors, cancers as well as other diseases. Examples of various tumors and cancers include Lymphoblastic Leukemia, Myeloid Leukemia, Adrenocortical Carcinoma, Hepatocellular Cancer, Liver Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma, Soft Tissue Sarcoma, AIDS-related Maglinancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Tumors, Breast Cancer, CNS Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Medulloblastoma, Pancreatic Cancer, Endometrial Cancer, Ewing's Sarcoma, Gastric Cancer, Germ Cell Tumors, Gestational Trophoblastic Tumors, Hairy Cell Leukemia, Head and Neck Cancer, Intraocular Melonoma, Hypopharyngeal Cancer, Intestinal Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lung Cancer, Osteosarcoma, Skin Cancer, Retinoblastoma, Rhabdomyosarcoma, Thyoma,… etc.

Thus, the scope of claim 31 is unduly broad. Claims 33 and 34 depend on claim 31, and thus, also share the same unduly broad scope.

The amount of direction or guidance presented: The claimed compound inhibits epidermal growth factor receptor (EGFR), erbB2, erbB4. Said receptors are found in cancers such as: breast, ovarian, colorectal, prostate and lung cancer. The specification does not provide data or evidence on reduction of tumor size or cell growth for other cancers that are not related to the cited receptors. Neither the prior art nor the instant disclosure establishes a nexus between the inhibition of said receptors and the treatment of the various types and forms of cancer associated with proliferative effects.

The state of the prior art: The claimed compound is commercially known as Iressa or Gefitinib which, in a preclinical studies, is shown to treat cancers such as: prostate, ovarian, breast, colon, small-cell and non-small-cell lung, and ductal carcinoma. Even for the listed cancers, "only tumors in which inhibition of the receptor results in inhibition of down stream signaling pathways are growth arrested." (see page 861 (right column), **Grünwald V. et. al.**, REVIEW, J. Nat. Can. Inst., Vol. 95, No. 12, 6/18/03). Thus, the state of the art does not correlate the inhibition of EGFR to all types of cancers as encompassed by the "proliferative effect". Therefore, the state of the art does not support the scope of the claimed method.

The relative skill of those in the art: There has never been a compound capable of treating cancer generally, let alone treating all kinds of cancers related to "proliferative effect". Different types of cancers affect different organs and have different modes of growth and harm to the body as well as different vulnerabilities. Thus, the existence of such a "silver bullet" is

contrary to our present understanding in oncology. Therefore, it is beyond the skill of oncologists today to get an agent to be effective against all cancers caused by proliferative effect in general.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the showing of EGFR inhibition alone does not guarantee the compound's effectiveness in treating cancers that are not related to EGFR.

See ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Thus, given the unpredictable nature of the art, and the preliminary research in the art, one skilled in the art will have to carry out undue experimentation to practice the method of treatment recited in claims 31, 33 and 34. When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, ***In re Ferens***, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal requires undue experimentation, ***Genetech vs. Novo Nordisk***, 42 USPQ 2nd 1001, 1006.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 1-29 and 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Moore et. al.** (US 7,160,891 B2) in view of **Lohmann et. al.** (US 5,962,458).

In US'891, Lohmann et. al. disclose several compounds in column 47, specifically the compound on lines 34-36 is analogous to those of the instant formula I with the following substituents:

i. A is phenyl;

ii. R^1 is alkoxy and halogen; m = 2;

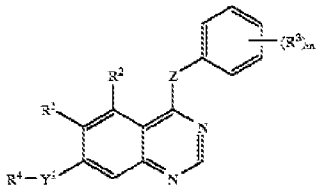
iii. R^3 is hydrogen; n = 0;

iv. R^4 does not exist;

v. R^5 and R^6 are alkyl.

Said compound differs from the claimed compound by having an *alkylenyl-O-* chain between the pyrrolidinyl ring and the benzo ring, and a substituent at the 5-position, and not at the 6-position. However, such a difference can be remedied by the teaching of **Lohmann et. al.** (US'458). In column 2 of US'458, Lohmann et. al. disclose formula (I) which has substitution at 6- and 7- positions. The substituent at the 7-position is R^4-Y^1-, wherein Y^1 can be –O-, and R^4 is a heterocyclic group which could be substituted with -C(O)-$NR^{12}R^{13}$. See the following excerpt:

(I)



[wherein:
Y^1 represents —O—, —S—, —CH_2—, —SO—, —SO_2—, —NR^5CO—, —$CONR^5$-, —SO_2NR^7-, —NR^8SO_2— or —NR^9- (wherein R^5, R^6, R^7, R^8 and R^9 each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl);
R^1 represents hydrogen, hydroxy, halogeno, nitro, trifluoromethyl, cyano, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, or $NR^{10}R^{11}$ (wherein R^{10} and R^{11}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl);
R^2 represents hydrogen, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, cyano, amino or nitro;
m is an integer from 1 to 5;
R^3 represents hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino or nitro;
R^4 is selected from one of the following eight groups:
1) X^1 (wherein X^1 represents a pyridone group, a phenyl group or a 5 or 6-membered aromatic heterocyclic group with 1 to 3 heteroatoms selected from O, N and S, which pyridone, phenyl or heterocyclic group may carry up to 5 substituents selected from halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, cyano, —$CONR^{12}R^{13}$ and —$NR^{14}COR^{15}$ (wherein R^{12}, R^{13}, R^{14} and R^{15}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

Thus, one skilled in the art would have been motivated to place the *pyrrolidinyl* ring directly linked to the *oxygen* (i.e., *pyrrolidinyl-O-*) because such a modification would have maintained the same biological activity for the compound as VEGF inhibitors.

Thus, at the time of the invention, it would have been obvious to make and use compounds of the instant formula I in view of the combined teachings above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tamthom N. Truong/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

10-22-09